PUBLIC HEALTH LABORATORY SERVICE

(Directed by the Medical Research Council for the Ministry of Health)

Central Enteric Reference Laboratory & Bureau

~~CENTRAL PUBLIC HEALTH LABORATORY~~

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2nd April, 1953.

Dear Dr. Lederberg,

As usual I start with an apology for having delayed the reply to your letter of March 8th, as I have been away from the laboratory. I have read your letter with great interest and shall now try to answer a few of the points you have raised.

1). Reversion of strain 0901 to the O + H variant - I was reassured to read what you said about the "mutation rate" for H reversion in strain 0901, and that you thought this would be negligible in routine laboratory practice. As recently as 1951 (J.Hyg. 1951, 49, on page 94) I stated that "no reversion to the motile O + H form has yet been observed" - yet, your exacting selective technique has so soon shown this statement not to be correct. I wonder what figure you would give to the "mutation rate" of the two subcultures of 0901 which I recently sent you.

I was also interested to read that you have found other "O-variants" much less stable than 0901. I had not come across any typhoid "O-variant" comparable in stability to that of strain 0901. Whenever an apparent O form was encountered, in my own or in some other laboratory, it invariably behaved in the way I first described in the Journal of Immunology, 1924, 9, on pages 156-157.

Similarly, I was cheered up by your statement that the "BO" strain that is widely used for routine serum diagnosis is still less susceptible to H reversion. Dr. Stocker, for whom we examined recently various cultures from his transduction experiments for their reactions to our typing phages, also mentioned this a few days ago. I do not know whether Edwards' no. 13 Ky. Bull. 54, 1942 is identical with my "BO" strain, or whether it is one of Kauffmann's cultures. If it is a typhi-murium strain and labelled "BO", it probably is the strain referred to in the Lancet, 1930, i, 505. This strain belongs to Vi-phage Type 1a of Salm. typhi-murium, according to our provisional typing scheme, which is to be published (with Miss Callow). On the other hand, Kauffmann had an "O" strain of Group B, labelled F.K.248, which is Salm.para-typhi B, Vi-phage Type "Jersey", according to the typing scheme published in the Lancet, 1951, 2, 10. ✓ = Salm. Bute.

2). O antigens as phage receptors - I am not at all optimistic as to the possibility of linking the action of certain phages to a particular component of the complex O antigens of the various Salmonellae. I certainly had

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no intention of doing so in Table 1 of the Oxford Symposium. Quite contrary, my intention was to indicate that the "so-called typhoid anti-O phages" act far beyond the four components IX, XII_1, XII_2, XII_3 which, according to Kauffmann, constitute the whole, or at least the major part, of the O-antigen complex of Salm. typhi. To express this I listed in Table 1 under the heading "Antigens" the following: "IX, XII_1, XII_2, XII_3 and many other O-antigen components." Obviously, the table has been badly arranged if it appears to you to convey the impression that "XII_1, XII_2, XII_3" are considered to be specific receptors for certain phages.

I think your query "Or is the classification of these components so crude an over-simplification as to vitiate any such enterprise?" (see last sentence of paragraph 2 on page 2 of your letter of March 8th) should be answered with a clear-cut "Yes". This is true in spite of the seemingly minute differentiation of the Salmonella O antigens presented in the Kauffmann-White Schema. The same applies to some of the other Groups of Gram-negative organisms (Bact. coli, etc.). On the other hand in the Proteus group there is much less overlapping in the various O antigens.

Edwards' experience with XII_2 in Salm. pullorum strains, which you have mentioned, is in good agreement with what I wrote in my previous letter regarding quantities of antigen so small that they may not be demonstrable by any serological test in vitro, but only by immunization of rabbits. Incomparably smaller amounts of antigen may be sufficient to act as phage receptors.

3). H antigens - A few words regarding the induction or selection of variants showing "unsuspected (?)" cross reactions, which you discussed in your letter. I am afraid you and your co-workers will soon encounter more of these "unsuspected" reactions. For instance, as long ago as 1920 Weil and I showed by hyper-immunization of rabbits that Salm. typhi may contain a minute amount of the H antigen of Salm. enteritidis (Ztschr. Immun. Forsch., 29, 24; see tables 39 and 40 on page 74). Within the next few weeks I shall have to prepare a brief paper describing the occurrence, in minute quantity, of the Salm. typhi H antigen (d) in a strain of Salm. paratyphi B. (Kindly treat this information as confidential for the time being.)

These are quite "illegitimate" findings according to the Kauffmann-White Schema, and they have no practical effect in routine laboratory practice since the most refined agglutination or agglutinin-absorption tests will not detect these small amounts of antigen. On the other hand, these observations naturally are of significance in the work on transduction and induction of antigenic properties which you have inaugurated. I shall not be surprised if in the course of this work the Kauffmann-White Schema is not found to be an entirely trustworthy guide.

4). H agglutination of formolized suspensions - I am interested in your finding that the c phases obtained from Salm. kunzendorf are agglutinated by the corresponding H agglutinin when examined in the live state, but that the reaction is impaired by the customary formalin treatment. I am rather puzzled to know what may be the mechanism involved.

You are probably familiar with the fact that the H antigen, when present in formolized or phenolized suspensions, inhibits the reaction between the O antigen and the O antibody (Felix and Olitzki, 1928, J. Hyg. Camb., 28, 55).

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No satisfactory explanation of the phenomenon has yet been found. Craigie's (1931, J.Immunol., 21, 417) suggestion that the hardened flagella mechanically separate the body of the bacteria and thus inhibit O agglutination cannot be correct, because Vi agglutination of formolized suspensions is not inhibited in the presence of flagella (Felix, 1938, J. Hyg. 38, see page 761). I wonder whether the hypothesis of mechanical hindrance could provide a plausible explanation of the inhibition of a poorly-developed H component which is overshadowed by the large amount of other H antigens present.

5). Inagglutinability of suspensions heated at 75°C. - Thank you for your interesting suggestion of the possible effect of the release of nucleic acids. I have not yet had time to look up the Italian paper of which you gave a partial reference.

6). Professor Crézé followed your suggestion and wrote some weeks ago. The information he gave me was probably the same he had sent you before. I also followed your advice and took Crézé's letter very seriously, as you will see from the attached copy which I am sending for your information.

7). You referred to Landy's experiments bracketed with those of Booy and Wolff. Landy was the American worker whom I first mentioned in connection with "transduction" of Vi antigen in mouse experiments (in my letter of the 1st January, 1953, on page 2). I have not seen any published paper of Landy's and I have not heard from him recently. I assume that Landy may have read a paper at some meeting or that he communicated his results personally to you.

Although I am rather slow in writing letters I wish to assure you that I much enjoy this correspondence. I take it for granted that you will be attending the Rome Congress this year and I am looking forward to the pleasure of meeting you there.

With kind regards,
Yours sincerely,

A. Felix

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